

# Vectorcardiographic QRS area is associated with long-term outcome after cardiac resynchronization therapy



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**BACKGROUND** Recent studies have suggested that vectorcardiographic measures predict left ventricular (LV) reverse remodeling and clinical outcome in patients receiving cardiac resynchronization therapy (CRT).

**OBJECTIVES** The objectives of this study were to compare predictive abilities of different vectorcardiographic measures (QRS area and sum absolute QRS-T integral) and transformation methods (Kors and inverse Dower) and to assess the independent association between the best predictor and outcomes in CRT recipients.

**METHODS** This retrospective study included CRT recipients with a digital baseline electrocardiogram, QRS duration  $\geq 120$  ms, and ejection fraction  $\leq 35\%$ . The end point was a composite of heart transplantation, LV assist device implantation, or all-cause death. Analyses were performed for the overall cohort and for a prespecified subgroup of patients with left bundle branch block (LBBB).

**RESULTS** Of 705 included patients with a mean age of  $66.6 \pm 11.5$  years, 492 (70%) were men, 374 (53%) had ischemic heart disease, and 465 (66%) had LBBB. QRS area from vectorcardiograms derived

via the Kors transformation demonstrated the best predictive value. In multivariable Cox regression, patients with a smaller QRS area ( $\leq 95$   $\mu$ Vs) had an increased hazard in the overall cohort (adjusted hazard ratio 1.65; 95% CI 1.25–2.18  $P < .001$ ) and in the LBBB subgroup (adjusted hazard ratio 1.95; 95% CI 1.38–2.76  $P < .001$ ). QRS area was associated with outcome in patients with QRS duration  $< 150$  ms (unadjusted hazard ratio 3.85; 95% CI 2.02–7.37  $P < .001$ ) and in patients with QRS duration  $\geq 150$  ms (unadjusted hazard ratio 1.76; 95% CI 1.32–2.34  $P < .001$ ).

**CONCLUSION** Vectorcardiographic QRS area is associated with survival free from heart transplantation and LV assist device implantation in CRT recipients.

**KEYWORDS** Cardiac resynchronization therapy; Heart failure; Left bundle branch block; QRS area; QRS duration; Sum absolute QRS-T integral; Vectorcardiography

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## Introduction

Although cardiac resynchronization therapy (CRT) has been an established treatment for patients with prolonged QRS duration

and heart failure for several years,<sup>1–3</sup> a substantial proportion of patients do not benefit from the treatment.<sup>4,5</sup> In current guidelines, QRS morphology and duration are the 2 surrogates

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of dyssynchrony used for patient selection.<sup>6</sup> Recently, 2 different vectorcardiographic measures of dyssynchrony have been proposed, namely, QRS area and sum absolute QRS-T integral (SAI QRS-T), and these have been shown to identify delayed activation of the left ventricular (LV) lateral wall, predict echocardiographic response to CRT, and, in a small retrospective cohort study, predict survival after CRT.<sup>7-10</sup> Currently, there are no published comparisons of these 2 vectorcardiographic measures or the different matrices (the Kors matrix and the inverse Dower matrix) used for the derivation of the vectorcardiogram from the digital 12-lead electrocardiogram (ECG).<sup>11,12</sup>

The objectives of this study were to compare the predictive abilities of the 2 different vectorcardiographic measures and the 2 transformation matrices and to assess the association between the best predictor and long-term outcome in CRT recipients.

## Methods

This was a retrospective cohort study performed at Duke University Medical Center. The study was approved by the Duke Health Institutional Review Board and complies with the Declaration of Helsinki.

## Study population

All patients who received CRT with defibrillator from April 1, 2006 to September 30, 2015 were identified using an institutional data set prepared for the National Cardiovascular Data Registry. We included patients who received a de novo CRT owing to symptomatic heart failure with LV ejection fraction  $\leq 35\%$  and had an ECG available with QRS duration  $\geq 120$  ms within 180 days before CRT implantation.

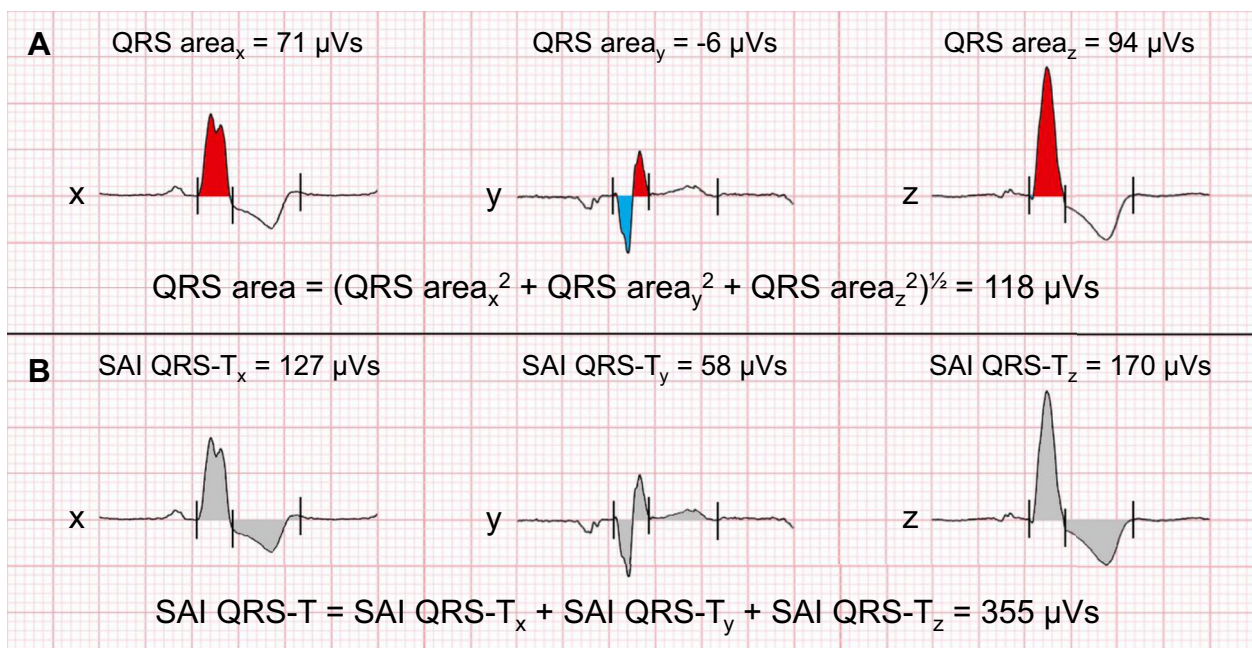
Patients were excluded if the LV lead could not be implanted, the patient demonstrated second- or third-degree atrioventricular block, or the patient had missing follow-up data.

## Electro- and vectorcardiographic analyses

The ECG most proximal to CRT implantation was reanalyzed in the MUSE Cardiology Information System version 8.0.2.10132 with 12SL analysis software version 241 (GE Healthcare, Milwaukee, WI) and exported in Extensible Markup Language (XML) format. QRS morphology was designated by 2 readers (D.J.F. and K.E.) blinded to outcome. Left bundle branch block (LBBB) morphology was further divided into strict and nonstrict LBBB using the criteria described by Strauss et al.<sup>13</sup> QRS onset and offset and thereby QRS duration as detected using 12SL software were verified or manually corrected if needed.

Vectorcardiograms were derived from the XML files using customized MATLAB software (MathWorks, Inc., Natick, MA) using both the inverse Dower and Kors matrices.<sup>11,12</sup> Using the median beat, QRS area and SAI QRS-T were calculated as described previously by others.<sup>8,9</sup> QRS area was calculated as  $(QRS_x^2 + QRS_y^2 + QRS_z^2)^{1/2}$ , with  $QRS_{x/y/z}$  being the integral between the ventricular deflection and the baseline from the onset to the offset of the QRS complex in the x, y, and z leads, respectively (Figure 1A). SAI QRS-T was calculated as the sum of the absolute areas between the deflection and the baseline of the entire QRS-T waveform from the x, y, and z leads (Figure 1B). Thus, a total of 4 vectorcardiographic measures were derived:

1. QRS area (Kors)
2. QRS area (inverse Dower)
3. SAI QRS-T (Kors)
4. SAI QRS-T (inverse Dower)



**Figure 1** Examples of calculation of QRS area and SAI QRS-T from the vectorcardiogram. **A:** QRS area is calculated using the integral between the deflection and baseline from the onset to the offset of the QRS complex. **B:** SAI QRS-T is calculated as the sum of the orthogonal leads' absolute area under the QRS complex and T-wave deflections. The vertical lines mark the onsets and offsets of the QRS complex and the T-wave offset. SAI QRS-T = sum absolute QRS-T integral.

## End points

The study end point was a composite of heart transplantation, LV assist device implantation, or all-cause death. End point ascertainment was performed on May 24, 2017, via a query of the Duke Enterprise Data Unified Content Explorer by incorporating data from billing claims, hospital records, and the Social Security Death Index.<sup>14</sup>

## Statistical analyses

Continuous normally distributed variables are reported as mean  $\pm$  SD and differences were tested using the Student *t* test, while nonnormally distributed variables are reported as median (25th–75th percentile) and differences were tested using the Wilcoxon rank-sum test. Categorical variables were compared using the Fisher exact test.

Time-dependent receiver operating characteristic (ROC) curves were created to assess the ability of the 4 vectorcardiographic measures to predict the occurrence of the study end point and the vectorcardiographic measurement with the largest area under the curve (AUC) at 3 years after CRT implantation was used for all subsequent analyses. The median value for the overall cohort was used to separate cohorts into 2 groups.

Kaplan-Meier plots were used to depict the cumulative hazard of the composite outcome and differences were

assessed using log-rank statistics. Cox proportional hazard models were used for assessing univariable and multivariable predictors of the composite outcome. Multivariable models were adjusted for ischemic heart disease, QRS morphology, QRS duration  $<150$  ms, atrial fibrillation/flutter, and univariable predictors with a *P* value of  $<.10$ . Proportional hazards assumptions were verified graphically using plots of Schoenfeld residuals. Sensitivity analysis with stepwise removal of the covariates in the model was performed. Analyses were performed for the overall cohort and for the prespecified subgroups of patients with LBBB and non-LBBB QRS morphologies.

All statistical analyses were performed in RStudio version 1.1.423 (RStudio, Inc, Boston, MA) running R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The R packages “survival”<sup>15</sup> and “time-ROC”<sup>16</sup> were used for survival analyses and time-dependent ROC curves. A 2-sided *P* value of  $<.05$  was considered statistically significant.

## Results

A total of 1001 patients underwent CRT implantation at Duke University Medical Center during the study period. After excluding patients with a missing baseline digital ECG (*n* = 159, 16%), prior LV lead (*n* = 12, 1%), QRS duration

**Table 1** Baseline characteristics of the overall cohort

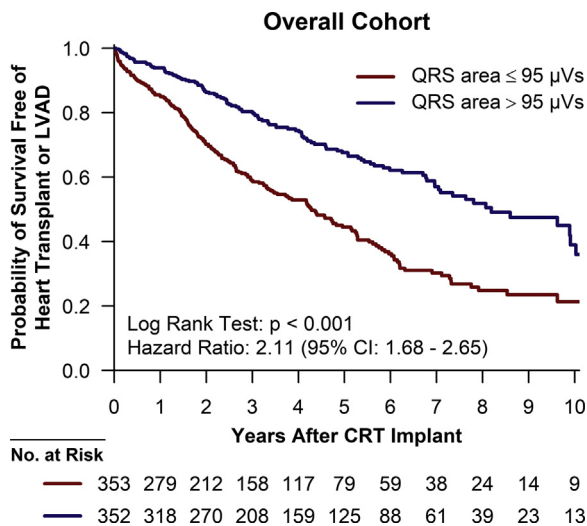
Characteristic	All (N = 705)	QRS area $\leq 95$ $\mu$ Vs (n = 353)	QRS area $> 95$ $\mu$ Vs (n = 352)	<i>P</i>
Days from ECG to CRT*	6 (1–23)	7 (1–24)	5 (1–22)	.22
Age (y)	66.6 $\pm$ 11.5	66.4 $\pm$ 10.9	66.7 $\pm$ 12.2	.76
Male sex	492 (70)	270 (76)	222 (63)	$<.001$
Ischemic heart disease	374 (53)	216 (61)	158 (45)	$<.001$
LVEF (%)	24 $\pm$ 7	24 $\pm$ 7	24 $\pm$ 7	.69
NYHA class III/IV	584 (83)	309 (88)	275 (78)	.001
QRS duration (ms)	163 $\pm$ 27	153 $\pm$ 25	174 $\pm$ 26	$<.001$
QRS duration $<150$ ms	239 (34)	186 (53)	53 (15)	$<.001$
QRS morphology				
Strict LBBB	358 (51)	120 (34)	238 (68)	$<.001$
Nonstrict LBBB	107 (15)	85 (24)	22 (6)	$<.001$
RV paced	119 (17)	38 (11)	81 (23)	$<.001$
RBBB	27 (4)	26 (7)	1 ( $<1$ )	$<.001$
RBBB + LAFB	49 (7)	44 (12)	5 (1)	$<.001$
RBBB + LPFB	5 (1)	5 (1)	0	.06
Nonspecific IVCD	40 (6)	35 (10)	5 (1)	$<.001$
PR interval (ms)	186 $\pm$ 40	193 $\pm$ 44	179 $\pm$ 34	$<.001$
First-degree AV block	118 (17)	78 (22)	40 (11)	$<.001$
Atrial fibrillation/flutter	243 (34)	127 (36)	116 (33)	.43
Hypertension	513 (73)	259 (73)	254 (72)	.74
Diabetes	266 (38)	144 (41)	122 (35)	.10
Cerebrovascular disease	89 (13)	51 (14)	38 (11)	.17
Chronic lung disease	151 (21)	83 (24)	68 (19)	.20
Creatinine level (mg/dL)*	1.2 (1.0–1.6)	1.3 (1.0–1.6)	1.1 (0.9–1.4)	$<.001$
Creatinine level $>1.2$ mg/dL	323 (46)	186 (53)	137 (39)	$<.001$
ACE inhibitor/ARB	540 (77)	260 (74)	280 (80)	.10
$\beta$ -Blocker	627 (90)	300 (86)	327 (93)	.002
Diuretics	583 (84)	295 (85)	288 (82)	.41

Data are presented as mean  $\pm$  SD or as n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; AV = atrioventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; IVCD = unspecific intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.

\*Values are presented as median (25th–75th percentile), and the Wilcoxon rank-sum test was used for statistical testing.





**Figure 2** Kaplan-Meier plot of event-free survival for the overall cohort. The curves are in relation to QRS area above (blue) or below (red) the median value 95  $\mu$ Vs. The hazard ratio is unadjusted. CI = confidence interval; CRT = cardiac resynchronization therapy; LVAD = implantable left ventricular assist device.

<120 ms ( $n = 56$ , 6%), LV ejection fraction >35% ( $n = 17$ , 2%) or missing ( $n = 7$ , <1%), failed LV lead ( $n = 8$ , <1%), second- or third-degree atrioventricular block ( $n = 34$ , 3%), or missing follow-up data ( $n = 3$ , <1%), a total of 705 patients remained. Of the included patients, 492 (70%) were men, the mean age was  $66.6 \pm 11.5$  years, 374 (53%) had ischemic heart disease, 465 (66%) had LBBB, and the mean QRS duration was  $163 \pm 27$  ms (Table 1).

### Predictive ability of vectorcardiographic measurements

The Kors-derived QRS area predicted the probability of reaching the study end point 3 years after CRT implantation better than did the inverse Dower-derived QRS area (AUC 0.645 vs 0.620;  $P = .005$ ), and SAI QRS-T derived by either the Kors method (AUC 0.645 vs 0.625;  $P = .03$ ) or the inverse Dower method (AUC 0.645 vs 0.608;  $P = .001$ ) (Supplemental Figure 1). Based on these results, the Kors-derived QRS area was used for all subsequent analyses.

### Patient characteristics by QRS area

The median (25th–75th percentile) QRS area derived by the Kors method for the overall cohort was 95  $\mu$ Vs (63–127  $\mu$ Vs). Patients with QRS area  $\leq 95$   $\mu$ Vs were more often men with ischemic heart disease, more advanced New York Heart Association functional class, longer PR interval, shorter QRS duration, higher serum creatinine level, and were less likely to receive  $\beta$ -blocker medication. Patients with QRS area >95  $\mu$ Vs were more likely to have strict LBBB or have right ventricular pacing, whereas all other QRS morphologies were more common in patients with QRS area  $\leq 95$   $\mu$ Vs (Table 1).

### Follow-up

Over a median follow-up of 3.1 years (25th–75th percentile 1.8–5.4 years), 312 patients (44%) reached the study end

point. The most common reason for reaching the end point was death ( $n = 263$  [37%]) followed by LV assist device implantation ( $n = 26$  [4%]) and heart transplantation ( $n = 23$  [3%]). During follow-up, 194 patients with QRS area  $\leq 95$   $\mu$ Vs (55%) experienced an end point as compared with 118 patients with QRS area >95  $\mu$ Vs (34%) (Figure 2). QRS area was associated with the likelihood of reaching the study end point in both univariable (unadjusted hazard ratio 2.11; 95% confidence interval [CI] 1.68–2.65;  $P < .001$ ) and multivariable analyses adjusting for QRS duration and morphology, age, sex, ischemic heart disease, first-degree atrioventricular block, atrial fibrillation/flutter, LV ejection fraction, New York Heart Association functional class, creatinine level, cerebrovascular disease, chronic lung disease, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use, and  $\beta$ -blocker use (adjusted hazard ratio 1.65; 95% CI 1.25–2.18;  $P < .001$ ) (Table 2).

### QRS area and outcomes in LBBB and non-LBBB subgroups

The median QRS area for the LBBB subgroup was 101  $\mu$ Vs, while it was 77  $\mu$ Vs for the non-LBBB subgroup ( $P < .001$ ). In the LBBB subgroup, 260 of 465 patients (56%) had QRS area >95  $\mu$ Vs. The baseline characteristics for the LBBB subgroup are described in Supplemental Table 1. Among patients with QRS area  $\leq 95$   $\mu$ Vs, 109 (53%) reached the composite end point as compared with 77 patients with QRS area >95  $\mu$ Vs (30%) (unadjusted hazard ratio 2.35; 95% CI 1.75–3.15;  $P < .001$ ) (Figure 3A). In the adjusted model including the same covariates as the model for the overall cohort, QRS area remained significantly associated with the composite outcome (adjusted hazard ratio 1.95; 95% CI 1.38–2.76;  $P < .001$ ) in patients with LBBB.

Among patients without LBBB, QRS area >95  $\mu$ Vs was much more common in patients with right ventricular pacing (81 of 119 [68%]) than all other non-LBBB QRS morphologies (11 of 121 [9%]). QRS area  $\leq 95$   $\mu$ Vs was associated with the study outcome in univariable analysis (unadjusted hazard ratio 1.55; 95% CI 1.07–2.25;  $P = .02$ ) (Figure 3B). After adjusting for QRS duration and morphology, age, sex, ischemic heart disease, and atrial fibrillation/flutter, QRS area was not significantly associated with the study end point (adjusted hazard ratio 1.50; 95% CI 0.94–2.39;  $P = .09$ ) in patients without LBBB. Among patients without non-LBBB and without right ventricular pacing, QRS area  $\leq 95$   $\mu$ Vs demonstrated a nonsignificant association with worsened outcomes (unadjusted hazard ratio 2.76; 95% CI 0.86–8.80;  $P = .09$ ).

### Outcome in relation to QRS area in combination with QRS duration

In patients with QRS duration <150 ms, 53 of 239 (22%) had QRS area >95  $\mu$ Vs. In patients with QRS duration  $\geq 150$  ms, 167 of 466 (36%) had QRS area  $\leq 95$   $\mu$ Vs. In the LBBB subgroup, 51 of 185 patients with QRS duration <150 ms (28%) had QRS area >95  $\mu$ Vs and 71 of 280 patients with QRS

**Table 2** Association of QRS area and baseline variables to outcome in univariable and multivariable analyses for the overall cohort

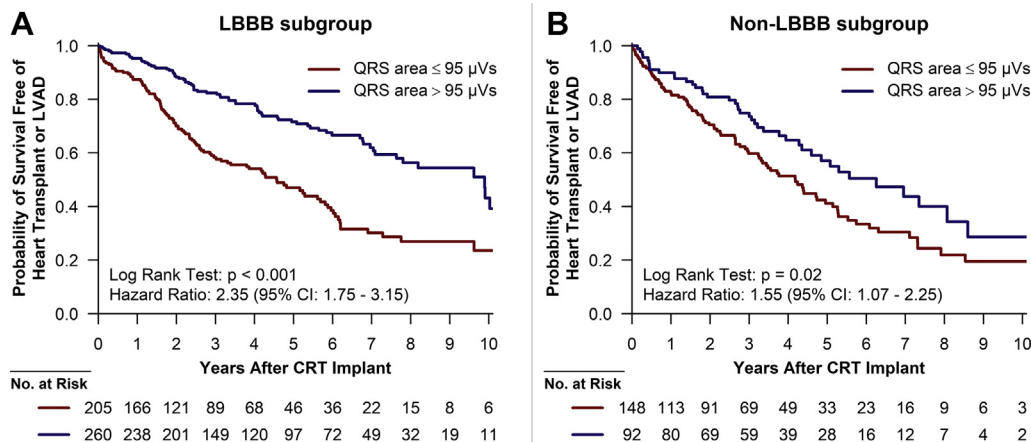
Variable	Univariable Cox regression			Multivariable Cox regression		
	HR	95% CI	P	HR	95% CI	P
Age (per 5-y increase)	1.05	1.00–1.10	.05	0.98	0.93–1.04	.54
Male sex	1.61	1.23–2.11	<.001	1.00	0.73–1.36	.99
Ischemic heart disease	1.69	1.34–2.12	<.001	1.35	1.04–1.75	.03
QRS duration <150 ms	1.44	1.14–1.81	.002	1.27	0.91–1.77	.15
QRS morphology						
Strict LBBB	(1.00)			(1.00)		
Nonstrict LBBB	1.66	1.22–2.27	.001	0.87	0.58–1.31	.51
RV paced	1.49	1.10–2.02	.01	1.17	0.82–1.67	.38
Nonspecific IVCD	2.04	1.33–3.14	.001	1.06	0.65–1.72	.83
RBBB + LAFB	1.31	0.83–2.06	.24	0.49	0.30–0.80	.005
RBBB + LPFB	19.97	7.91–50.39	<.001	6.96	2.66–18.20	<.001
RBBB	2.01	1.13–3.56	.02	1.19	0.64–2.22	.59
First-degree AV block	1.63	1.24–2.13	<.001	1.79	1.33–2.41	<.001
Atrial fibrillation/flutter	2.00	1.59–2.50	<.001	1.64	1.28–2.12	<.001
LVEF (per 5% increase)	0.91	0.84–0.99	.03	0.91	0.83–1.00	.05
Hypertension	1.13	0.87–1.45	.36			
Diabetes	1.18	0.94–1.48	.15			
NYHA class III/IV	1.90	1.28–2.82	.001	1.49	0.99–2.26	.06
Creatinine level >1.2 mg/dL	2.39	1.90–3.00	<.001	1.86	1.44–2.40	<.001
Cerebrovascular disease	1.50	1.11–2.02	.009	1.23	0.90–1.70	.19
Chronic lung disease	1.72	1.35–2.20	<.001	1.39	1.07–1.80	.01
ACE inhibitor/ARB	0.44	0.34–0.56	<.001	0.57	0.44–0.74	<.001
$\beta$ -Blocker	0.57	0.41–0.78	<.001	0.78	0.56–1.10	.16
Diuretics	1.23	0.87–1.74	.24			
QRS area $\leq 95$ $\mu$ Vs	2.11	1.68–2.65	<.001	1.65	1.25–2.18	<.001

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; AV = atrioventricular; CI = confidence interval; HR = hazard ratio; IVCD = unspecific intraventricular conduction delay; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block; RV = right ventricular.

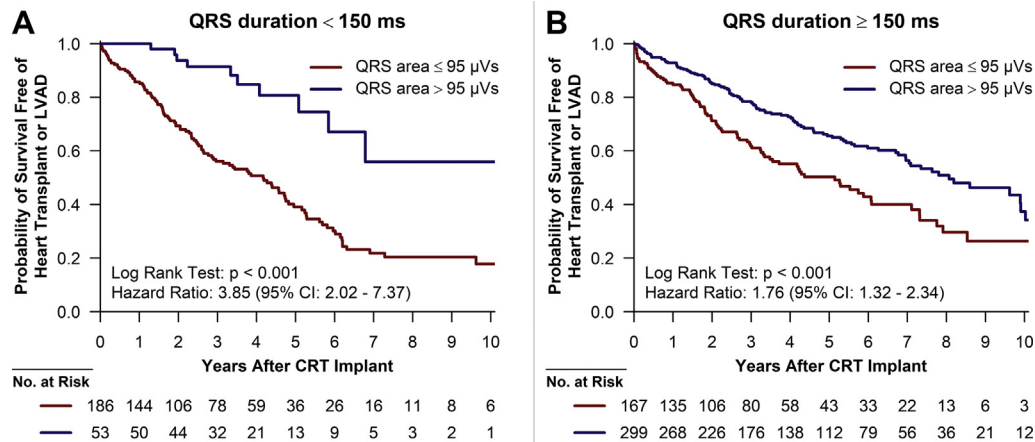
duration >150 ms (25%) had QRS area  $\leq 95$   $\mu$ Vs. QRS area  $\leq 95$   $\mu$ Vs was associated with the study end point in univariable analysis in both patients with QRS duration <150 ms (unadjusted hazard ratio 3.85; 95% CI 2.02–7.37;  $P < .001$ ) (Figure 4A) and patients with QRS duration  $\geq 150$  ms (unadjusted hazard ratio 1.76; 95% CI 1.32–2.34;  $P < .001$ ) (Figure 4B). Similar results were found in the LBBB subgroup when stratifying by QRS duration below or above 150 ms (Supplemental Figure 2).

## Discussion

First, this study found that a smaller baseline QRS area calculated from derived vectorcardiograms is associated with an increased hazard of death, heart transplantation, or LV assist device implantation after CRT independently of critical baseline characteristics such as QRS duration and morphology. Second, the study found that the Kors method is superior to the inverse Dower method in the derivation of the



**Figure 3** Kaplan-Meier plots of event-free survival for the LBBB (A) and non-LBBB (B) subgroups. The curves are in relation to QRS area above (blue) or below (red) 95  $\mu$ Vs. The hazard ratios are unadjusted. CI = confidence interval; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LVAD = implantable left ventricular assist device.



**Figure 4** Kaplan-Meier plots of event-free survival for QRS duration below (A) or above (B) 150 ms for the overall cohort. The curves are in relation to QRS area above (blue) or below (red) 95  $\mu\text{Vs}$ . The hazard ratios are unadjusted. CI = confidence interval; CRT = cardiac resynchronization therapy; LVAD = implantable left ventricular assist device.

vectorcardiogram for prediction of CRT outcome using QRS area. Third, it found that among the 2 most widely studied vectorcardiography-based measures of LV electrical delay, QRS area is superior to SAI QRS-T in the prediction of adverse outcomes after CRT implantation. Finally, the study findings suggest that especially in patients with QRS duration  $<150$  ms (ie, patients without a current class I indication for CRT), QRS area has important prognostic value.

### Vectorcardiographic measures as predictors of CRT outcome

Vectorcardiography was developed in the 1950s but has been seldom used clinically for the past 20 years. With the development of digital ECG signal processing, renewed interest in vectorcardiography has emerged, largely as a tool for patient selection in CRT. The digital 12-lead ECG allows the digital derivation of a vectorcardiogram that bears good resemblance and correlation with vectorcardiograms recorded using Frank's method.<sup>17,18</sup> Prior studies have demonstrated that QRS area identifies delayed LV lateral wall activation in CRT candidates, while SAI QRS-T correlates with a dyssynchrony index determined by noninvasive ECG mapping.<sup>7,19</sup> Thus, these measures were proposed to reflect LV electrical dyssynchrony and thereby identify a substrate amenable to CRT. Subsequent studies demonstrated that QRS area and SAI QRS-T predicted LV reverse remodeling and long-term outcome after CRT.<sup>8–10</sup>

### Current guidelines for the selection of CRT candidates

Currently, QRS duration and morphology are the only ECG measures incorporated in guidelines for the selection of CRT candidates.<sup>6</sup> The presence of LBBB and QRS duration  $\geq 150$  ms are associated with a high likelihood of a positive outcome after CRT implantation.<sup>20–23</sup> However, this study found that within this cohort of patients with a current class I indication for CRT,<sup>6</sup>  $\sim 25\%$  have QRS area  $\leq 95 \mu\text{Vs}$  and

an increased hazard of adverse outcome after CRT implantation. In addition, this study finds that QRS area is strongly associated with long-term outcome in patients with QRS duration  $<150$  ms both in the overall cohort and in the LBBB subgroup, that is, patients without a current class I indication for CRT.

Strict vs nonstrict LBBB was a predictor of outcomes in unadjusted analyses; however, in adjusted models, strict vs nonstrict LBBB was not a significant predictor, in contrast to QRS area, which remained a robust predictor of outcomes. Taken together, these data suggest that QRS area is a more powerful predictor of outcomes than is strict vs nonstrict LBBB.

In patients without LBBB, a smaller QRS area was also associated with an increased hazard of adverse outcome in univariable analysis. However, the association was not significant in multivariable analysis, albeit the estimated hazard ratio was not changed much (from 1.55 in univariable analysis to 1.50 in multivariable analysis). In patients without LBBB or right ventricular pacing,  $<10\%$  had QRS area  $>95 \mu\text{Vs}$ . Nevertheless, there was a trend toward these patients having a substantially better outcome than similar patients with QRS area  $\leq 95 \mu\text{Vs}$ . As the LV has a significantly larger myocardial mass than does the right ventricle, QRS area is mainly determined by electrical activation in the LV and is thought to reflect LV dyssynchrony. The results of this study suggest that an important minority of patients with non-LBBB QRS morphology may have LV activation delay, which might be amenable to correction using CRT. However, owing to the lack of statistical power in these exploratory analyses, further research is needed.

### Study limitations

The major limitation of this study is the retrospective nature and absence of a control group. To definitively establish that QRS area effectively identifies CRT candidates, studies that include a control group of patients not receiving CRT are needed. Vectorcardiography may simply identify patients with a high risk of

adverse outcomes regardless of whether they benefit from CRT, for example, by identifying patients with extensive myocardial scarring. Neither this study nor the previously mentioned studies<sup>8–10</sup> included a control group who did not receive CRT, and despite efforts to adjust for confounding, the risk of residual confounding is inherent in the study design.

It is possible that the use of transformed 12-lead ECGs rather than vectorcardiograms may have led to patient misclassification. However, a prior study has shown good agreement between these methods,<sup>17</sup> and furthermore, 12-lead ECGs (and not vectorcardiograms) are ubiquitous in clinical practice.

Because of the relatively small study cohort, we were unable to separately test and validate the QRS area threshold in separate subpopulations. The findings should be replicated in a prospective study to confirm the predictive value of vectorcardiographic QRS area.

This study included only a clinical end point, and no data on LV reverse remodeling or symptomatic improvement were available. However, previous studies have shown that QRS area is associated with LV reverse remodeling and acute hemodynamic response to CRT.<sup>8,24</sup> In addition, the single-center nature of the study may decrease the generalizability of results.

Data on several device attributes and parameters were not included in our adjusted models, including LV lead type and position, percent biventricular pacing, and whether CRT optimization was performed. Finally, since many patients undergo CRT implantation at Duke University Medical Center but have routine longitudinal care via referring providers, comprehensive data on postimplantation device programming and management were not available.

## Conclusion

Derived vectorcardiographic QRS area is independently associated with survival free from heart transplantation and LV assist device implantation regardless of QRS duration and presence of LBBB. QRS area calculated from vectorcardiograms derived using the Kors method is superior to QRS area derived using the inverse Dower method and to SAI QRS-T from vectorcardiograms derived using either method.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2018.08.028>.

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